Title:

Physiological effects of millimeter-waves on skin and skin cells: An overview of the to-date published studies

Short Title:

Effect of mm-waves on skin

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ABSTRACT

The currently ongoing deployment if the 5th generation of the wireless communication technology, the 5G technology, has reignited the health debate around the new kind of radiation that will be used/emitted by the 5G devices and networks – the millimeter-waves. The new aspect of the 5G technology, that is of concern to some of the future users, is that both, antennas and devices will be continuously in a very close proximity of the users' bodies. Skin is the only organ of the human body, besides the eyes, that will be directly exposed to the mm-waves of the 5G technology. However, the whole scientific evidence on the possible effects of millimeter-waves on skin and skin cells, currently consists of only some 99 studies. This clearly indicates that the scientific evidence concerning the possible effects of millimeter-waves on humans is insufficient to devise science-based exposure limits and to develop science-based human health policies. The sufficient research has not been done and, therefore, precautionary measures should be considered for the deployment of the 5G, before the sufficient number of quality research studies will be executed and health risk, or lack of it, scientifically established.

KEYWORDS

5G technology; millimeter-waves; skin; precautionary approach; limited deployment;

INTRODUCTION

The currently ongoing deployment of the 5th generation of the wireless communication technology (5G) is being met with a great enthusiasm by the telecommunication industry, national governments and portion of the general public. However, there is also some resistance from the part of the population in various locations around the globe.

The opposition towards the deployment of the 5G is caused by the uncertainty whether radiation emitted by the 5G networks and devices will have any effects on human health and environmental impact on fauna and flora.

The 5G wireless communication technology that is being deployed comprises of parts of the used already 3G and 4G technologies. The radiation emitted by the predecessors of the 5G, the radiation frequencies emitted by the 3G and 4G technologies, has been classified by the International Agency for Research on Cancer (IARC), as possible human carcinogen. The IARC evaluation did not concern the frequencies above 6 GHz, especially the currently prepared for use 26 GHz and 28 GHz bands and the whole spectrum of 30 – 300 GHz frequencies that will be used in coming years. The currently deployed 5G will be supplemented with a new technology that uses the millimeter-waves (mm-waves) for the fast transfer of large amounts of data. Right now, the 5G technology expands into the frequencies below the 6 GHz. Later on, the 5G will use also the frequencies of 6 – 30 GHz and, still later on, frequencies of mm-waves (30 – 300 GHz). Currently, in Europe, the spectrum of 26 GHz (range 24.25 – 27.5 GHz) and 28 GHz (range 26.5 – 29.5 GHz), is being freed for the 5G use.

It is well established that the 26 GHz and 28 GHz frequencies and mm-waves penetrate only few millimeters inside the human body and are efficiently absorbed by the water content of dermis layer of the skin. This fact has been used to misleadingly portray mm-waves as unlikely affecting the physiology and health of human body because the depth of penetration is only skin deep and does not reach any internal organs.

THE QUESTION

Do we know enough about the interactions between skin and skin cells with mm-waves to determine what health impact, if any, will have the acute and the long-term (life-time) exposure of skin to mm-waves?

In order to answer the question, literature search was performed to find studies where skin and skin cells were examined following exposure to mm-waves and affected functions and properties of skin and skin cells were evaluated in the context of the possible impact, or lack of it, on human health.

In this brief opinion review is presented evidence on the physiological effects of mm-waves exposures on human volunteers, on laboratory animals and on human and animal cells grown in the laboratory.

THE SKIN

In the research examining the effects of mm-waves, skin is simplified into three major components, the stratum corneum consisting of mostly dead cells, the epidermis consisting of few layers of cells where the bottom layer is made of dividing cells that continuously regenerate the epidermis and the underlying dermis layer. The water content of the skin is what determines the depth of penetration of the mm-waves into human body, limiting it to just couple of millimeters.

From the point of view of water content of the skin, the top layer of the skin, the stratum corneum, has low water content 15–40%), whereas the water content the rest of the skin, epidermis and dermis, is ca. 70–80%. Thus, mm-waves energy penetrates the stratum corneum but is efficiently and effectively absorbed by the water in epidermis and dermis layers [1].

Skin is the largest organ of human body that not only functions as kind of “overcoat” but is involved in regulation of physiological processes that impact the functioning of the whole body.

Skin has different thickness, color, and texture in different locations over the body and performs number of important functions. Skin (i) regulates immune response by both mechanically preventing entry of microorganisms and biochemically by generation of molecular mediators that are distributed with blood circulation to internal organs (ii) regulates body temperature, (ii) stores water and fat and prevents water loss, (iii) functions as sensory organ, and (vii) helps to make vitamin D when exposed to the sunlight.

Skin is composed of a variety of cell types that perform various functions. In epidermis reside keratinocytes, melanocytes, Merkel cells, and Langerhans cells. The dermis consists of connective tissue cells and extracellular matrix and there are located numerous nerve endings that provide the sense of touch and heat, the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. Furthermore, the skin surface provides an environment for over thousand identified species of microbes.

Different pathological conditions affecting skin might have impact on how the skin and skin cells perform their functions and how they might react/respond to mm-waves exposure. These skin ailments, that will affect levels of water in the skin, include dermatitis, eczema, psoriasis, dandruff, acne, cellulitis, skin abscess (boil or furuncle), rosacea, warts, melanoma, basal cell carcinoma, seborrheic keratosis, actinic keratosis, squamous cell carcinoma, herpes blisters, hives, tinea versicolor, viral exantham, shingles, herpes zoster, scabies, or ringworm [2].

Therefore, skin is not just a thin overcoat on the surface of the human body but it is an aggregate of numerous cells and microorganisms living together and playing a crucial role in regulating of the health and wellbeing of human body. As Sanford and Gallo [3] pointed out in their review article:

> “...*The skin, the human body’s largest organ, is home to a diverse and complex variety of innate and adaptive immune functions […] the skin immune system should be considered a collective mixture of elements from the host and microbes acting in a mutualistic relationship*...”

LITERATURE SEARCH

Databases search: Articles have been selected from the following science databases: PubMed (www.ncbi.nlm.nih.gov/pubmed), EMF-Portal (https://www.emf-portal.org/) and ORSAA (https://www.orsaa.org/orsaa-database.html). The following keywords or combinations of keywords were used: “millimeter waves”, “skin”, “human”, “mice”, and “rats”. Studies presenting effects of mm-waves on skin physiology and on skin-dependent and skin-induced whole body physiology were analyzed. Peer reviewed original experimental studies published in the English language until September 2019 were considered.

Conflict of interest: Author state no conflict of interest.

Ethical approval: The conducted research is not related to either human or animals use.

BRIEF REVIEW OF THE PUBLISHED STUDIES

The to date published studies examining the effects of millimeter waves on the skin and skin cells provide very haphazard and lacking consistency picture of the possible/probable effects. However, the lack of replications and small size of the studies hamper the efforts to determine whether the skin exposures to millimeter-waves will, or will not, have any physiologically meaningful effects on human health.

I. HUMAN VOLUNTEER STUDIES

Table 1 lists 11 studies performed on human volunteers. There are suggestions that the mm-waves might affect skin and several skin properties that might play a role in how the skin responds to mm-waves’ exposures:

- Hydration level of the skin, as water efficiently absorbs mm-waves [4, 5]
- Thickness of the skin regulates penetration of the mm-waves, in part due to the mm-waves absorbing content of the water in dermis layer [5]
- Distribution and density of distribution of the sweat glands that were proposed to act as structural antennae for the mm-waves [6, 7, 8]
- Distribution of the acupuncture sites and pain/pressure sensing sites that appear to respond to mm-waves [9, 10, 11, 12]
- Health status of the skin that compromises normal functioning of the skin, e.g. psoriasis or skin cancer [5]

This very limited evidence provided in just an 11 human volunteer studies suggests possibility of differences in skin responses depending on the anatomical location of the exposed skin on the individual’s body as well as differences between individuals due to differences in individuals’ skin properties. Also, there is a suggestion that the health status of the skin might affect responses of the skin to mm-waves exposure.

There is a single study where the authors claim to, in their own words, “rule out” any effects of skin exposure to mm-waves on the heart rate, EKG, blood pressure on respiration [13]. However, the scientific significance of the evidence of this single study appears to be overstated by the authors and further experiments are necessary to determine the potential effects of skin exposure to mm-waves on cardiovascular system in humans. Execution of such studies, examining effects of human skin exposure to mm-waves on the functioning of the cardiovascular system, is justified because some of the experimental studies in animals indicate that skin-exposure-derived effects on cardiovascular system might be possible (for details see later in animal studies section).

II. ANIMAL IN VIVO STUDIES

Tables 2A and 2B list in vivo animal studies performed in rats and mice, respectively. The majority of studies on effects of mm-waves on skin and skin cells was published in in vivo animal studies, using rat and mice models. Exposure of hairless areas (naturally or shaven) of the skin of mice and rats was able to induce effects in distant internal organs that were not in any way exposed to mm-waves. This was likely through secretion of yet to be identified molecular mediators that were generated and secreted by the skin cells exposed to mm-waves and transported to distant internal organs with e.g. blood circulation or via nerve endings of the skin.

RAT MODEL

Skin morphology and gene expression

- Morphology: aggregation of neutrophils in vessels, degeneration of stromal cells, and breakdown of collagen [15]
- Gene expression: affected genes associated with regulation of transcription, protein folding, oxidative stress, immune response, tissue matrix turnover and chemokine activity [15]

Rat brain and nervous tissue

- Prevention of epileptic attacks, suggested to be resulting from absorption of mm-waves in skin [16]
- Molecular effects in rat brain, resulting from the absorption of mm-waves in hairless areas of the skin. Decline in activity of protein kinase C, superoxide dismutase and glutathione peroxidase but an increase in catalase activity. Simultaneously occurred an increase in DNA double-strand breaks [17]
- Effect of heated-skin-mediated impact on whole body stress and brain EEG [18]
- Acceleration of nerve regeneration following surgically-induced injury [19]
- Painful electrical stimulation-induced decline in splenic NK cell activity was prevented by co-exposure of skin to mm-waves [20]

Rat sperm

- Molecular effects of oxidative stress were observed in sperm of rats, decline in histone kinase, and catalase activity but increase in superoxide dismutase and glutathione peroxidase. Concomitantly occurred increase in apoptosis and decline in S/G2/M phase in spermatocytes, suggesting possible impact on male fertility [21]

- Degeneration and polymorphism of spermatozoa, deformation of the head and filaments. Number of progeny of irradiated rats increased and was associated with the presence of abnormal spermatozoa [22]

Rat skin overheating impact on circulatory system

- Rapidly elevated temperature of skin, even when the rectal temperature appears normal, may cause circulatory failure [23, 24]
- Histopathological changes in the skin (hemorrhage, congestion of skin blood vessels) and molecular changes serum glucose, creatinine and uric acid. Rapid heating of skin led to circulatory failure and death [25, 26, 27, 28]
- Circulatory effects were not mediated by the levels of nitric oxide, regulated using L-NAME inhibitor of nitric oxide synthesis [29, 30]

Right- and left-polarized mm-waves

- Both, left-handed and right-handed-polarized mm-waves induced small changes in bone-marrow derived leukocytes, erythrocytes and their hemoglobin content. Effects of the right-handed-polarized, but not the left-handed-polarized, mm-waves were diminished by shielding with schungite (mineral rock with C_{60} structure similar to fullerens) [31]
- Both polarizations exerted different effects on stomachs of rats. Right-handed-polarization increased activity of pepsin and suppressed production of mucin and caused hypertrophy of secreting structures in stomach mucosa. Left-handed-polarization caused decline in pepsin production, secretory activity was suppressed, gastric mucosa was covered with mucus occurred necrotic changes, hemorrhaging and occlusion of small blood vessels and epithelium lost microvilli [32]

Rat tissue oxidative stress

- mm-waves exposure that elevates colonic temperature but does not cause hypotension, was associated with increase expression of oxidative stress marker, 3-nitrotyrosine, in lung, liver and blood plasma, leukocytes, intestine and kidney [33]
- Increase/decrease in antioxidant enzymes activity (superoxide dismutase, glutathione peroxidase, catalase) observed in blood leukocytes and blood serum, in brain tissue and in sperm, what suggests defensive response to increased levels of reactive oxygen species [17, 21, 34]

Skin-secreted molecular mediators of macrophages

- Plasma from mm-waves-exposed rats increased expression of 11 proteins, and levels of 3-nitrotyrosine in seven proteins (associated with inflammation, oxidative stress, and energy metabolism) [35]

MICE MODEL

Regulatory impact on immune processes

- Cancer-related effects
    - Regulates (inhibition/enhancement) growth of transplanted tumor cells [36]
    - Does not co-promote, with TPA, development of papilloma in DMBA-induced mice [37]
    - Inhibition of the sub-cutaneous growth of injected B16 melanoma cells [38]
- Impact of mm-waves on cyclophosphamide-related effects
    - Inhibition of cyclophosphamide-induced activation of anti-apoptotic mediator NF-kB [39]
    - No genotoxic effect (no generation of micronuclei) and no effect on cyclophosphamide-induced micronuclei [40]
    - Lack of effect on cyclophosphamide-induced toxic effect on catalase activity [41]
    - Lack of effect on cyclophosphamide-induced toxic effects on leukocytes and bone marrow [42]
    - Restoration of cyclophosphamide-inhibited activity of NK cells [43]
    - Inhibition of cyclophosphamide-induced metastasis due to prevention of cyclophosphamide-induced inhibition of NK cell activity [44]
    - No impact on therapeutic (anti-cancer) properties of cyclophosphamide [45]
    - Restores CD25 expression on CD4+ T cells and increases generation of IFNγ but not IL-10. Effector function of CD4+ T cells is enhanced via Th1 type of immune response (IFNγ). Inhibit effects of CPA by augmenting the proliferation of splenocytes, and altering the activation and effector functions of CD4+ T cells [46]
    - Restores cyclophosphamide-inhibited generation of TNFα, increases generation of IFNγ and T-cell proliferation. No effect on IL10 or B-cell proliferation [47]
    - Restores cyclophosphamide-inhibited generation of Th1 cytokines TNF-α, IFN-γ, and IL-2 and shifts balance of T cells from Th2 towards the pre-cyclophosphamide treatment Th1 [48]
    - Restores phagocytic activity and proliferation of T-cells that were inhibited by cyclophosphamide [49]
    - Inhibits scratching activity of mice induced by pruritogenic agent (compound 48/80) and naloxone suppresses this effect suggesting involvement of endogenous opioids [50]

Regulation of inflammation

- Anti-inflammatory effects by affecting generation of arachidonic acid metabolites and histamine [51, 52]
- Induction/restores changes in composition of fatty acids in thymic cells [53, 54, 55]
- In mice with ongoing inflammation, reduces inflammation and inhibits generation of reactive oxygen species [56]
- Changes in content of CD4+ and CD8+ T-cells in thymus and spleen and changes in expression of cytokines: of IL-1β, IFNγ in thymus and IL-1β, IL-10, and TNFα in spleen [57]

Whole-body well being

- Enhances survival/development of mouse-embryos in vitro [58]
- Had no effect on several health-related parameters: body mass, body temperature, peripheral blood, and mass and cellularity of several important organs like spleen, thymus, adrenal glands, skin, cornea [59]

Effects on muscles and nerves

- Inhibited spontaneous electric activity of sural nerve. Cessation of mm-waves exposure briefly increased nerve firing rate. Depletion of mast cells abolished the mm-waves-effect [60]
- Induces contraction of muscle without temperature increase (non-thermal effect) [61]

Hypoalgesisa and anesthesia

- Induction of hypoalgesic effect due to release of endogenous opioids [62] and lack of effect on small intestinal or colonic transit [63]
- Hypoaglesic effect was stronger when exposed skin is more densely innervated (nose, footpad) [64] but unilateral transection of sciatic nerve abolishes hypoaglesic effect [65]
- Suppresses chronic non-neuropathic pain. Hypoalgesic effect was not mimicked by temperature increase what might suggest non-thermal effect [66]
- Extend the length of anesthesia and opioid antagonist, naloxone, abolishes the effect [67]
- Extends tail-flick period and the effect is blocked by naloxone, what suggests involvement of endogenous opioids [68]

III. HUMAN CELLS IN VITRO STUDIES

Table 3 lists human in vitro studies. There are some 26 studies that examined effects of mm-waves on human skin-residing cells such as: buccal cells, fibroblasts, glial cells, primary keratinocytes and keratinocyte cell line, lymphocytes and melanoma cells. Results obtained by different research groups vary, showing both, some effects or lack of effects of MMW exposure.

Buccal cells

- Shckorbatow et al. [69, 70] have observed changes in chromatin condensation that may suggest effect on activity of genes and on gene transcription process

Fibroblasts

- Shckorbatow et al. [71] observed an increase in granularity of the chromatin in fibroblasts, occurring in a radiation dose dependent manner. Furthermore, the effect was radiation polarization-dependent, where right-handed polarization had stronger effect than the left-hand polarization
- On the other hand, Yakeshiwa et al. [72] has shown lack of effects on proliferation and toxicity of fibroblasts
- Also Gallerano et al. [73] have shown lack of effects on a variety of cytogenetic markers in fibroblasts

Glial cells

- Nicolaz et al. [74, 75] and Zhadobov et al. [76] have shown lack of effect on cellular stress markers and on protein folding, secretion and maturation in endoplasmic reticulum

Primary cultures of keratinocytes

- Bourne et al. [77] did not detect any effect on stress response by monitoring expression of glutathione and Hsp70
- Le Quement et al. [78] analyzed expression of 41000 genes using microarray assay. Depending on the statistical analysis applied to the data, the result was either no effect at all (Benjamini-Hochberg procedure) or effect on some 130 transcripts (t-test). Further analysis of these t-test-indicated potentially affected transcripts by RT-PCR has shown that 24 proteins were indeed affected by the MMW exposure. This observation points out that some of the statistical analyses may incorrectly dismiss changes in expression of genes, especially when the changes are small in magnitude.
- Habauzit et al. [79] observed an effect on gene expression that, according to the authors, suggests a specific electromagnetic effect of mm-waves as the effects was not possible to mimic solely by altering temperature of the cells
- Soubere Mahmoud et al. [80], similarly to Habauzit et al. [79], also did not observe any direct effect of MMW exposure on the transcriptome. However, they observed that mm-waves exposure might affect cells that are under metabolic stress

Keratinocyte cell line HaCaT

- Chen et al. [81] observed lack of effect of MMW exposure on cell-cell communication via gap junctions. However, mm-waves exposures appeared to reverse suppression of gap junction communication induced by phorbol ester. Similarly, lack of effect on gap junction communication was observed by Szabo et al. [82]

- Szabo et al. [82, 83] observed lack of exposure on cell viability, proliferation, adhesion, chemotaxis, interleukin production, expression of stress protein Hsp70. Similarly, Zhadobov et al. [84] did not observe effect of MMW exposure on cell proliferation, gene expression of the conformation of proteins
- Using HaCaT keratinocytes as well as mouse melanoma cells B16F10 and Jurkat cells, Szabo et al. [85] observed the mm-waves-exposure-induced externalization of phosphatydylserine residues on cell membranes, occurring without visible cell membrane damage. Expression of phosphatydyl serine, an early marker of apoptosis, in combination with the observed lack of damage to cell membrane, suggests that biological processes induced by mm-waves exposures could be initiated by the molecular changes induced in cell membranes. Similarly, Le Pogam et al. [86] have observed effect of mm-waves exposures on the permeability of cell membranes
- Le Quement et al. [87] have shown that while mm-waves exposure does not induce endoplasmic reticulum stress markers of BIP and ORP150, it is able to prevent expression of these markers that was induced by thapsigargin. This points out to potential co-exposure effects of mm-waves exposures
- An important marker of the potentially detrimental effect of radiation exposure is a damage to chromosomes and chromatin. Hintzsche et al. [88] examined effects of mm-waves exposure on DNA strand breaks and presence of micronuclei and observed lack of an effect

Lymphocytes

- Using primary dividing lymphocytes, Korenstein-Ilan et al. [89] observed mm-waves-exposure-induced changes in several chromosomes number and replication and suggested that exposures induce genomic instability, a cancer risk factor
- Beneducci et al. [90] using stable leukemia cell line have observed very extensive changes in leukaemia cell morphology and in glucose metabolism

Melanoma cells

- In two separate studies by Beneduci et al. [91, 92], the effects of mm-waves exposure differed from each other. Using the same melanoma cell line RPMI 7932, in the first study, there was observed an anti-proliferative effect of mm-waves exposure whereas in the second study mm-waves exposure did not affect cell proliferation or cell cycle distribution of cells

IV. ANIMAL CELLS IN VITRO STUDIES

Table 4 lists animal in vitro studies.

In rat, neuron-like cells were examined in studies by Haas et al and the non-thermal mm-waves exposures did not affect:

- Expression of expression of neuronal phenotype marker β3-Tubulin nor ubiquitous β-Tubulin [93]
- Dopamine turnover or expression of dopamine transporter DAT protein [94]
- Expression of HSP70, Transient Receptor Potential cation channel subfamily Vanilloid, members 1 and 2 (TRPV1, TRPV2), and purinergic receptor P2X, ligand-gated ion channel, 3 (P2x3) [95]

In rat bone marrow stem cells, Tong et al [96] observed enhancement of the differentiatio by co-exposures to mm-waves and β-mercaptoethanol.

In mice, studies on co-cultures of carcinoma cells with keratinocytes and studies using various kind of leukocytes examined effects of mm-waves exposures.

- In mouse embryonal stem-cell-derived neuronal cells (P-19) mm-waves exposure induced calcium spiking that was dependent of the N-type calcium channels, phospholipase C enzyme. Exposure to mm-waves-induced reorganization of actin-fiber cytoskeleton played a role in regulation of calcium spiking and in regulation of cell size and shape (biomechanics of the cell) [97]
- In co-cultures of mouse embryonal stem-cell-derived neuronal cells (P-19) with keratinocytes, exposures to mm-waves induced increased calcium spiking and ATP secretion in keratinocytes. And the changes were dependent on the input power of the mm-waves [98]
- In neutrophils, mm-waves exposures inhibited or interfered with the process of generation of the reactive oxygen species [99, 100]. In peripheral blood leukocytes, mm-waves exposure had protective effect against DNA damage induced by e.g. X-rays, hydrogen peroxide or methylation agents [101]
- In neutrophils, mm-waves exposure enhanced response to N-formylmethionyl-leucyl-phenylalanine (fMLP) and the effect was modified by various kinase inhibitors [102]

DISCUSSION

The current use of the 3G and 4G technologies and the ongoing deployment of the 5G technology, where the number of base stations will increase dramatically, has reignited the health debate around the radiation emitted by these wireless communication technologies.

The new aspect of the 5G technology that will differ dramatically from the earlier technologies will be the use of mm-waves, where both, antennas and devices will be in very close proximity of the users, affecting the exposure patterns. In some countries, deployment of the 5G technology, using mm-waves for public use, has already begun what adds to the health-related stress of uncertainty in some part of the to-be exposed population.

When evaluating the health risk of any agent, the scientific evidence taken into consideration by the health regulatory authorities consists, in order of importance, of the following types of research studies:

- Epidemiology studies
- Human volunteer studies
- Animal in vivo studies
- Laboratory in vitro studies

The epidemiology studies are possible to execute only after the technology has been deployed and sizable parts of the population are being exposed to the examined agent, in this case the mm-waves radiation emitted by the 5G technology. Thus, this considered to be the most important and relevant scientific evidence is currently not available and will not be available for several years.

However, the remaining three types of studies are possible to execute, and should be executed, before the deployment of the 5G technology, in order to determine whether any risk of health effects exists.

Skin is the only organ of the human body, besides the eyes, that will be directly exposed to the mm-waves of the 5G technology. As presented in this review, the whole scientific evidence on the possible effects of mm-waves on skin and skin cells consists of only some 99 studies, where 11 are human volunteer studies, 54 are animal in vivo studies (rats & mice) and 34 are in vitro laboratory studies using human and animal cell cultures.

These studies examined only short-term acute effects of the exposure that do not provide any information about the possible delayed or long-term-exposure effects. Furthermore, the effects of mm-waves were examined in separation from other frequencies used by the wireless communication technologies and in separation from other environmental stressors. Possibility of any co-effects and/or synergistic effects, between mm-waves and other environmental stressors, were not examined at all.

This clearly indicates that the scientific evidence concerning the mm-waves effects on skin is extremely very limited. The evidence from the 99 studies is insufficient to make any reliable, science based evaluation of whether the mm-waves will have or will not have any health effects.

Besides the sheer number of executed studies, of importance in the analysis of the available scientific data are the types and number of performed studies, the size of the studies, the following of the good laboratory practices used when performing studies, whether the results obtained in one laboratory were possible to replicate by other research groups, and, finally, the number of the research groups that were involved in generation of the data. Scientific data from a single research group, no matter how extensive and well executed, need corroboration from other researchers. The research on mm-waves has been dominated by the research teams in Reims, France and in Philadelphia, USA, and their findings require replication studies from other research groups.

The very limited evidence, stemming from the 99 presented studies, suggests that some biological and physiologically relevant effects might be induced in skin and skin cells by exposures to mm-waves. However, this evidence is currently insufficient to claim that any effects have been proven or disproven.

Therefore, the usefulness of the to-date executed research on mm-waves effects on skin is of a very limited use because for developing protective measures for the users because:

- Firstly, as mentioned above, only a small number of studies examined mm-effects on skin and skin cells.
- Secondly, there is only a very few human volunteer studies.
- Thirdly, the majority of research are small experimental studies performed on animals (rats, mice) or cells grown in laboratory. While such studies are important, they are predominantly used to corroborate the evidence obtained in epidemiological and human volunteer studies. Results of animal and in vitro studies alone are not sufficient to formulate basis for human health policy and for human exposure limits.

Therefore, the recently published guidelines by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [103], stating that the ICNIRP proposed mm-waves radiation exposure limits are protecting users form health effects of mm-waves are only an assumption that is not sufficiently based on scientific evidence because the research on effects of mm-waves on skin has not been performed. This is why any claims, including ICNIRP's, that the current safety limits protect all users, no matter of their age or their health status, have no sufficient scientific basis. The safety limits that are suggested to protect from health effects of mm-waves are based on scientifically unsupported assumptions as seen from the evidence presented in Tables 1-4.

Another serious problem of how the 5G mm-waves employing technology is being presented to the future users is the misrepresentation of the role the skin plays in regulation of the whole body's physiology. The notion, often presented in the news media, that mm-waves will not be of health concern because mm-waves are entirely absorbed by epidermis and dermis layers, is misleading. Indeed, mm-waves are absorbed in the skin and do not penetrate deep enough to reach any internal organs. However, the skin is not just a "physiologically inert overcoat" shielding body from the environment. Skin is involved in regulation of the immune response as well as other body functions (cardiovascular functions, neurological functions) through release of a variety of molecular mediators generated by the skin cells in response to environmental stressors, like e.g. mm-waves.

Considering the very limited research on the effects of mm-waves on skin, there is an urgent need for research on effects of mm-waves on humans. Some of the studies is possible to execute, in ethical manner, using human volunteers. Toxicology studies, on mice and rats, using standardized protocols, like those used by the National Toxicology Program in USA, are urgently needed. In vitro laboratory studies should, preferably, use primary human cells or human cell lines. Studies using high-throughput screening techniques of transcriptomics, proteomics and metabolomics should be used to analyze the ethically available tissue samples obtained from human volunteers to determine the molecular level responses of human body to the mm-waves. Data obtained from the molecular high-throughput screenings can then be used to formulate research hypotheses for testing. Epidemiological studies might not be possible to execute as long as the 5G networks are not deployed and people are not exposed as a population.

Because of the lack of sufficiently robust scientific data on mm-waves effects on human skin, precautionary measures should be recommended, whenever possible and feasible when dealing with the mm-waves exposures. These precautionary measures can be e.g. postponing or limiting the 5G deployment in residential areas. It should be considered that not everything and not everywhere needs to be 5G wirelessly connected. Use of fiber optics connections, that will be used to connect 5G base stations, should be used as extensively as possible to limit the deployment of radiation-emitting devices, especially those in close proximity to people and within people dwellings. Deployment for industrial use should be the first but the further, broader deployment for the non-industrial use, should preferably await for the results of the bio-medical research.

Finally, as stated in recent opinions/reviews, the research on the possible effects of mm-waves on humans is scarce and inadequate for developing reliable, health protecting human health policies:

Foster, Ziskin & Balzano [104]

> "…*The frequency range above 3–10 GHz through the top of the RF band (300 GHz) has heretofore received relatively little attention by the committees that develop the guidelines, despite a large number of (generally low-powered) devices that already operate in this wide band […] However, this broad frequency band is about to gain much wider use with the introduction of a new generation (5G) of wireless communications […] and the development of high-powered millimeter wave devices (30–300 GHz) for industrial and military applications*…"

Wu, Rappaport & Collins [105]

> "...*Compared with lower frequency bands, relatively little careful research has been conducted evaluating the potential of more subtle long-term effects than tissue damage due directly to heating at mmWave frequencies*..."

CONCLUSION

In conclusion, there is an urgent need for research on the biological and health effects of mm-waves because, using the currently available evidence on skin effects, the claims that "*we know skin and human health will not be affected*" as well as the claims that "*we know skin and human health will be affected*" are premature assumptions that lack sufficient scientific basis.

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